



048007/30/01

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: Ewing et al.

Attorney Docket No.: CAMIP004

Application No.: 09/902,470

Examiner: UNASSIGNED

Filed: July 9, 2001

Group: UNASSIGNED

Title: ACCESSIBILITY CORRECTION FACTORS  
FOR ELECTRONIC MODELS OF  
CYTOCHROME P450 METABOLISM

**CERTIFICATE OF MAILING**

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail to: Commissioner for Patents, Washington, DC 20231 on July 27, 2001.

Signed:

Leslie Russell

**INFORMATION DISCLOSURE STATEMENT  
37 CFR §§1.56 AND 1.97(b)**

Commissioner for Patents  
Washington, DC 20231

Dear Sir:

The references listed in the attached PTO Form 1449, copies of which are attached, may be material to examination of the above-identified patent application. Applicants submit these references in compliance with their duty of disclosure pursuant to 37 CFR §§1.56 and 1.97. The Examiner is requested to make these references of official record in this application.

This Information Disclosure Statement is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that these references indeed constitute prior art.

This Information Disclosure Statement is: (i) filed within three (3) months of the filing date of the above-referenced application, (ii) believed to be filed before the mailing date of a first Office Action on the merits, or (iii) believed to be filed before the mailing of a first Office Action after the filing of a Request for Continued Examination under §1.114. Accordingly, it is believed that no fees are due in connection with the filing of this Information Disclosure Statement. However, if it is determined that any fees are due, the Commissioner is hereby authorized to charge such fees to Deposit Account 500388 (Order No. CAMIP004).

Respectfully submitted,

BEYER WEAVER & THOMAS, LLP

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Berkeley, CA 94704-0778


**Form 1449 (Modified)**
**Information Disclosure  
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	1A						

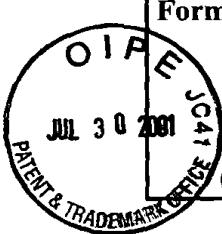
**Foreign Patent or Published Foreign Patent Application**

Examiner Initial	No.	Document No.	Publication Date	Country or Patent Office	Class	Sub-class	Translation	
							Yes	No
	1B	WO 95/18969	07/13/95	PCT				
	1C							

**Other Documents**

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	1D	Bradford, M. M., et al., "A Rapid and Sensitive Method for the Quantitation of Microgram Quantities of Protein Utilizing the Principle of Protein-Dye Binding," ANAL. BIOCHEM., (1976) 72:248-54
	1E	Burka, L. T., et al., "Mechanism of Cytochrome P-450 Catalysis. Mechanism of N-Dealkylation and Amine Oxide Deoxygenation," J. AM. CHEM. SOC., (1985) 107:2549-51
	1F	Burka, L. T., et al., "Mechanisms of Hydroxylation by Cytochrome P-450: Metabolism of Monohalobenzenes by Phenobarbital-Induced Microsomes," PROC. NATL. ACAD. SCI. USA (1983) 80:6680-4
	1G	Cleland, W. W., "Partition Analysis and the Concept of Net Rate Constants as Tools in Enzyme Kinetics," BIOCHEMISTRY, (1975) 14(14):3220-4
	1H	Cleland, W. W., "The Use of Isotope Effects to Determine Transition-State Structure for Enzymic Reactions," METHODS ENZYMOL., (1982) 87:625-41
	1I	Cupp-Vickery, J.R. et al., "Structure of Cytochrome P450eryF Involved in Erythromycin Biosynthesis," STRUCTURAL BIOLOGY, (1995) 2(2):144-53
	1J	Dinnocenzo, J. P., et al., "On Isotope Effects for the Cytochrome P-450 Oxidation of Substituted NN-Dimethylanilines," J. AM. CHEM. SOC., (1993) 115:7111-6
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	1M	Gonzalez, F.J., et al., "Expression of Mammalian Cytochrome P450 Using Puccinia Virus," METHODS ENZYMOL., (1991) 206:85-92
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	2A						

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#### Other Documents

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	2C	Grogan, J., et al., "Modeling Cyanide Release from Nitriles: Prediction of Cytochrome P450 Mediated Acute Nitrile Toxicity," CHEM. RES. TOXICOL., (1992) 5(4):548-52
	2D	Groves, J. T., et al., "Aliphatic Hydroxylation by Highly Purified Liver Microsomal Cytochrome P-450. Evidence for a Carbon Radical Intermediate," BIOCHEMICAL & BIOPHYSICAL RESEARCH COMMUNICATIONS (1978) 81(1):154-60
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	2K	Hasemann, C.A., et al., "Structure and Function of Cytochromes P450: A Comparative Analysis of Three Crystal Structures," STRUCTURE, (1995) 3(1):41-62
	2L	Hasemann, C.A., et al., "Crystal Structure and Refinement of Cytochrome P450terp at 2-3 Å Resolution," J. MOL. BIOL., (1994) 236:1169-85
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	3C	Heberger, K., "Linear Free Energy Relationships in Radical Reactions. II Hydrogen Abstraction From Substituted Toluenes by TERT-Butyl, TERT-Butoxyl and Tert-Butylperoxyl Radicals," J. PHYS. ORG. CHEM., (1994) 7:244-50
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	3E	Hjelmeland, L. M., et al., "Intramolecular Determination of Primary Kinetic Isotope Effects in Hydroxylations Catalyzed by Cytochrome P-450," BIOCHEM. BIOPHYS. RES. COMMUN., (1977) 76:541-9
	3F	Jones, J. et al., "Predicting The Rates And Regioselectivity of Reactions Mediated By The P450 Superfamily," METHODS IN ENZYMOLOGY, (1996) 272:326-35
	3G	Jones, J. P., et al., "The Separation of the Intramolecular Isotope Effect for the Cytochrome P-450 Catalyzed Hydroxylation of n-Octane into Its Primary and Secondary Components," J. AM. CHEM. SOC., (1987) 109(7):2171-3
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	3K	Karki, S.B., et al., "On the Mechanism of Amine Oxidations by P450," Xenobiotica, (1995), 25(7):711-24
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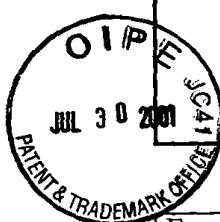
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	4B						No

**Other Documents**

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	4C	Karki, S.B., et al., "Mechanism of Oxidative Amine Dealkylation of Substituted N,N-Dimethylanilines by Cytochrome P-450: Application of Isotope Effect Profiles," J. AM. CHEM. SOC., (1995) 117(13):3657-64
	4D	Kim, S.S.; et al., "Comparative Hammett Studies of Imidoyl, Benzylic, Aldehydic Hydrogens Transfer and Related Reaction by t-Butoxyl Radical," TETRAHEDRON LETT., (1985) 26(7): 891-4
	4E	Kobayashi, Y., et al., "Probing the Active Site of Cytochrome P450 2B1: Metabolism of 7-Alkoxycoumarins by the Wild Type and Five Site-Directed Mutants," BIOCHEMISTRY, (1998) 37(19):6679-88
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	4H	Korzekwa, K.R., et al., "Predicting the Cytochrome P450 Mediated Metabolism of Xenobiotics," PHARMACOGENETICS, (1993) 3:1-18
	4I	Lindsay Smith, J.R., et al., "Model Systems for Cytochrome P450 Dependent Mono-Oxygenases. Part 2. Kinetic Isotope Effects for the Oxidative Demethylation of Anisole and [Me- <sup>2</sup> H <sub>3</sub> ] Anisole by Cytochrome P450 Dependent Mono-Oxygenases and Model Systems," J. CHEM. SOC. PERKIN TRANS. II, (1983) 5:621-8
	4J	Macdonald, T. L., et al., "Oxidation of Substituted N,N-Dimethylanilines by Cytochrome P-450: Estimation of the Effective Oxidation-Reduction Potential of Cytochrome P-450," (1989) BIOCHEMISTRY, 28:2071-7
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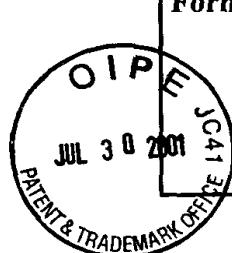
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	5C	Manchester, J.I., et al., "A New Mechanistic Probe for Cytochrome P450: An Application of Isotope Effect Profiles," J. AM. CHEM. SOC., (1997) 119:5069-70
	5D	Nelson, D.R., et al., P450 Superfamily: Update on New Sequences, Gene Mapping, Accession Numbers and Nomenclature, PHARMACOGENETICS, (1996) 6:1-42
	5E	Northrop, D.B., "Deuterium and Tritium Kinetic Isotope Effects on Initial Rates," METHODS ENZYML., (1982) 87:607-25
	5F	Northrop, D.B., "Steady-State Analysis of Kinetic Isotope Effects in Enzymic Reactions," Biochemistry, (1975) 14(12)2644-51
	5G	Omura, T., et al., "The Carbon Monoxide-Binding Pigment of Liver Microsomes," J. BIOL. CHEM., (1964) 239(7):2370-8
	5H	Poulos, T. L., et al., "High-Resolution Crystal Structure of Cytochrome P450cam," J. MOL. BIOL., (1987) 195:687-700
	5I	Ravichandran, K. G., et al., "Crystal Structure of Hemoprotein Domain of P450BM-3, a Prototype for Microsomal P450's," SCIENCE, (1993) 261:731-6
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	5L	Silver, E.H., et al., "Structural Considerations in the Metabolism of Nitriles to Cyanide In Vivo," DRUG METAB. DISPOS., (1982) 10(5):495-8
	5M	Smith, P. B., et al., "4-Ipomeanol and 2 Aminoanthracene Cytotoxicity in C3H11IOTll2 Cells Expressing Rabbit Cytochrome P450 4B1," BIOCHEM. PHARMACOL., (1995) 50(10):1567-75
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	6C	Szklarz, G. D., et al., "Site-Directed Mutagenesis as a Tool for Molecular Modeling of Cytochrome P450 2B1," BIOCHEMISTRY, (1995) 34:14312-22
	6D	Tassaneeyakul, W., et al., "Human Cytochrome P450 Isoform Specificity in the Regioselective Metabolism of Toluene and o-, m- and p-Xylene," J. PHARMACOL. EXP. THER., (1996) 276(1):101-8
	6E	Tyson, C. A., et al., "The Roles of Putidaredoxin and P450cam in Methylene Hydroxylation," J. BIOL. CHEM., (1972) 247(18):5777-84
	6F	Watanabe, Y., et al., "Kinetic Study on Enzymatic S-Oxygenation Promoted by a Reconstituted System with Purified Cytochrome P-450," TETRAHEDRON LETT., (1980) 21:3685-8
	6G	Westheimer, F. H., "The Magnitude of the Primary Kinetic Isotope Effect for Compounds of Hydrogen and Deuterium," CHEM. REV., (1961) 61(3):265-73
	6H	White, R. E., et al., "Oxygen Activation by Cytochrome P-450," ANN. REV. OF BIOCHEM., (1980) 49:315-56
	6I	White, R.E., et al., "Active Site Mechanics of Liver Microsomal Cytochrome P-450," ARCH. BIOCHEM. BIOPHYS., (1986) 246(1):19-32
	6J	White, R.E., et al., "Stereochemical Dynamics of Aliphatic Hydroxylation by Cytochrome P-450," J. AM. CHEM. SOC., (1986) 108: 6024-31
	6K	Wislocki, P.G., et al., "Reactions Catalyzed by the Cytochrome P-450 System," ENZYMATIC BASIS OF DETOXICATION, (1980) 1:135-82
	6L	Yin, H., et al., "Designing Safer Chemicals: Predicting the Rates of Metabolism of Halogenated Alkanes," PROC. NATL. ACAD. SCI. USA, (1995) 92(24):11076-80
	6M	Zerner, Michael C., "Semiempirical Molecular Orbital Methods," REVIEWS IN COMPUTATIONAL CHEMISTRY II, Chapter 8, 313-365 (1991)
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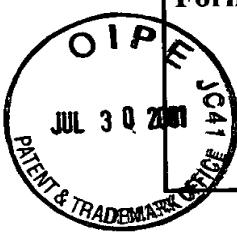
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	7B						

## Other Documents

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	7C	International Search Report for PCT/LTS99/17713 dated 11 November 1999
	7D	Abstract No. XP-002122407, P84 to Johnson et al., "Automated Modeling Predicts Active Site Geometries Consistent with the Regiospecificity of P450s 2C3v and 2C5 for Progesterone Hydroxylation," FASEB Journal 11(9):P785 (1997)
	7E	Korzekwa and Gillette, "Overview: Theoretical Aspects of Isotope Effects on the Pattern of Metabolites Formed by Cytochrome P-450," Biological Reactive Intermediates IV, Witmer et al., Eds. Plenum Press, NY (1990)
	7F	Korzekwa et al., "Theory for the Observed Isotope Effects from Enzymatic Systems that Form Multiple Products via Branched Reaction Pathways: Cytochrome P-450," Biochemistry 28: 9012 (1989).
	7G	
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